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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/636,530	08/10/2000	Thomas L. Cantor	532212000300	7117

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	

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DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/636,530	CANTOR, THOMAS L.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14, 16, 39, and 41-43, 45, 46 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,39,41-43,45,46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

The request filed on 21 October 2005 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/636,530 is acceptable, and a RCE has been established. An action on the RCE follows.

Applicant's amendment filed on 21 October 2005 is acknowledged and entered. Following the amendment, claims 44 and 47 are canceled, and claim 39 is amended.

Currently, claims 14, 16, 39, and 41-43, 45, 46 and 48 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 44 and 47 are moot as the applicant has canceled the claims.

The prior art rejection of claims 39, 41 and 42 under 35 U.S.C. 102(b) as being anticipated by Fukuda, EP 0 528 271 A1, is withdrawn in view of applicant's amendment.

The rejection of claims 39, 41-43, 45, 46 and 48 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

Formal Matters:

Claim 41 is objected to for the following informalities, appropriate correction is required for each item:

In line 2 of the claim, "SEQ ID NO:" is missing for PTH_{7-84}.

New Matter Rejection

Claim 39 and dependent claims 41-43, 45, 46 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly amended claim

recites the limitation "a subject diagnosed with hypoparathyroidism" (line 3), which reads on any or all species including human, and hypoparathyroidism of any or all causes. However, the specification merely discloses the experimental rats, which were parathyroidectomized. Such parathyroidectomized rats are hardly representative of all other species, nor their condition of "hypoparathyroidism" represents majority of clinical pathological conditions of hypoparathyroidism. Thus, the newly amended claim limitation has changed the scope of the invention, and is not supported by the original disclosure.

This is a new matter rejection.

Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 48 remains rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, and 21 April 2005.

Applicants argument filed on 21 October 2005 has been fully considered, but is not deemed persuasive for reasons below.

At pages 4-5 of the response, the applicant argues that to establish a rejection based on lack of utility, the Office must show that the claimed method does not provide a specific, substantial and credible utility, that the Office asserts that the claimed invention is inoperative based on a single reference describing a specific CPTH fragment, not discussing PTH antagonists commensurate with the scope of the present claims, and not recognizing that such compounds have the activity demonstrated by the data in the application, and that an inoperative embodiment within the claim scope does not even provide a basis for an enablement rejection. This argument is not persuasive for the following reasons. First, the specific CPTH fragment,

PHT-(7-84), used in the Divieti reference to demonstrate the distinct receptors for PTH antagonist is identical to that used for generating the data in the instant application. Second, the Divieti reference is specifically directed to the issue of receptor binding of the PTH antagonist, and demonstrates that PHT-(7-84) acts via receptors *distinct* from the PTH1R. In contrast, the data in the application is totally unrelated to receptor binding issue, and therefore, irrelevant to the limitation in claim 48. Finally, even though one reference is cited in the rejection, the instant specification provide none whatsoever as to evidence of receptor binding of PTH antagonists, or evidence of any kind contrary the findings of the art. Therefore, in the presence of the findings of the art, and the absence of evidence by applicants to the contrary, the claimed method remains inoperative, and therefore, it is not substantial.

Applicants further argue, on page 5 of the response, that the claim is drawn to the effect of a PTH antagonist of claim 39 at "a PTH binding site on a PTH receptor", it is not limited to a specific receptor or a specific antagonist, that it is credible that the PTH antagonists bind to other PTH receptors, and that even if the reference showed that the claim would not operate for one specific embodiment, the applicants focus on what is missing from the reference is believed to be proper and sufficient. This argument is not persuasive for the following reasons because the art has established so far that there is one PTH receptor, PTH1R, although it does not mean other PTH receptor(s) do not exist. Further, the Divieti reference indicates the distinct receptors for PTH antagonist with experimental data, whereas applicants argument is merely prophetic.

For the reasons above, the rejection of claim 48 under 35 U.S.C. 101 is maintained.

Claim 48 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for the same reasons above.

Claims 39 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for reducing calcium levels in a subject with secondary hypoparathyroidism resulted from elevated serum calcium levels, does not reasonably provide enablement for claims to a method for reducing calcium

levels in a subject with any type of hypoparathyroidism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 39 and 41-43 are directed to a method for reducing calcium levels in a subject with diagnosed with hypoparathyroidism, which reads on reducing calcium levels in any or all types of hypoparathyroidism. However, a search of the prior art reveals that one of the major causes of hypocalcemia is primary hypoparathyroidism (Beers et al., Merck Manual, 17th ed. (Jan. 1999), page 141-143), i.e., hypoparathyroidism usually results in *reduced* blood calcium levels. Only in the case of secondary hypoparathyroidism where the elevated serum calcium levels is the primary cause, PTH is suppressed due to the feedback mechanisms of hormone secretion. Therefore, it would be detrimental to further reduce blood calcium levels in subjects diagnosed with hypoparathyroidism that is accompanied with hypocalcemia. Therefore, those skilled in the art would not accept that the claimed method would be beneficial to such subjects. Further, the specification provides no guidance, nor working example as to how to use the claimed invention for treating hypoparathyroidism where blood calcium levels are below normal. Therefore, the invention is not commensurate in scope with the claims.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 39 and 41-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Slatopolsky et al. (Kidney Int. 2000 Aug; 58(2):753-61).

Slatopolsky discloses a PTH antagonist, PTH_{7-84}, teaches a method for reducing plasma calcium levels in animals with hypoparathyroidism using said antagonist, wherein rats were parathyroidectomized, and given PTH_{7-84} (in saline) in four doses of 5 ug each at 30-minute intervals (the paragraph bridging pages 755 and 756), and PTH_{7-84} is capable of reducing plasma calcium levels in these rats (Figure 5), which are "hypoparathyroidism". As such, the reference anticipates the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 and 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Takasu et al. (Endocrinology, 1996, 137(12): 5537-43), and Fukuda, EP 0 528 271 A1, for the reasons of record set forth in the previous Office Actions mailed on 13 September 2004, and 21 April 2005.

Applicants argument filed on 21 October 2005 has been fully considered, but is not deemed persuasive for reasons below.

At pages 8-9 of the response, the applicant argues that Fukuda provides no data for inhibition by N-terminally truncated peptides, and the data in Takasu demonstrates significant variability of efficacy for its peptides, depending on their length (Figure 5); and that neither reference suggests making the present composition of intermediate length, and nothing suggests that peptides of intermediate length are desirable or have superior activity or property. This argument is not persuasive for the following reasons. With respect to Fukuda provides no data, "a reference is not limited to the disclosure of specific working examples" *In re Mills*, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972). Further, according to MPEP (§2121), "when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d

675, 207 USPQ 107 (CCPA 1980)". In the instant case, Fukuda expressly teaches that the N-terminal truncated hPTH peptides function as antagonists of hPTH, and applicants provide no evidence to the contrary. With respect to Takasu's the data showing variability of efficacy for the peptides of different length, although there is certain degree of variability of binding efficacy, the efficacies of ALP activity among the peptides of different length are comparable (Figure 6). Further, this issue is less relevant because Takasu's peptides have the N-terminal deletions not within the range of the instantly claimed peptides. Furthermore, even if Takasu's the data had indicated unpredictability of the efficacy for the peptides of different length, the instant specification provides no evidence demonstrating that the claimed peptides, which have less truncation of the molecule than Takasu's peptides, would be unpredictable or would have variability of either binding or functional efficacy as merely one of the claimed peptides, PTH_{7-84}, had ever been tested (Figure 2). With respect to the argument that nothing in the cited references suggests that peptides of intermediate length are desirable or have superior activity or property, again applicants provide nothing either in this regard. Therefore, in the absence of any "unexpected" superior activity or property for the claimed peptides of intermediate length, mere argument is insufficient to overcome the rejection.

Applicants further argue, on page 9 of the response, that the office must provide reasoning for "it would be obvious"; that requirement is an important protection against impermissible hindsight reconstruction of the claimed invention; and that based on the reference one would have a hope of success rather than the requisite "reasonable expectation" of success. This argument is not persuasive because, as addressed in the last Office Action, Fukuda teaches hPHT antagonist comprising the N-terminal deletions of 3 to 6 residues, and Takasu teaches a hPHT antagonist with minimum size of the fragment hPTH(35-84), and clearly and obviously, the combined teachings of the cited references indicate a range of deletions, i.e., deletion can be made anywhere between amino acids 1-34 of hPTH in order to generate a PTH antagonist. With respect to the argument of "hindsight reconstruction", it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392,

170 USPQ 209 (CCPA 1971). With respect to the argument of "have a hope of success rather than the requisite 'reasonable expectation' of success", given the fact that both Fukuda's peptide with the N-terminal deletion of 3 residues, and Takasu's peptide with the N-terminal deletion of 34 residues are PTH antagonists, those of ordinary skill would have a reasonable expectation of success that, in the absence of evidence to the contrary, anything between such would be a PTH antagonist. Obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Claim 43 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Fukuda, EP 0 528 271 A1, for the reasons of record set forth in the previous Office Actions mailed on 13 September 2004, and 21 April 2005.

Claims 45 and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fukuda, EP 0 528 271 A1, as applied to claims 39, 41-44 and 47 above, and further in view of Kanmera et al., EP 0 451 867, for the reasons of record set forth in the previous Office Actions mailed on 13 September 2004, and 21 April 2005.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Dong Jiang, Ph.D.
Patent Examiner
AU1646
11/18/05